54. A method for the detection of a target nucleic acid molecule that encodes a protein comprising a polypeptide having the amino acid sequence of SEQ ID NO:3, 6, or 11 in a sample containing nucleic acids, the method comprising the steps of:

(a) contacting the nucleic acids with the nucleic acid molecule of claim 53 under conditions suitable for hybridization, and

(b) detecting a hybridization product.

55. A method for detection of a target nucleic acid molecule of claim 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, or 47 in a sample containing nucleic acids, the method comprising the steps of:

(a) contacting the nucleic acids with a probe nucleic acid molecule comprising a nucleotide sequence complementary to the target nucleic acid molecule under conditions suitable for hybridization, and

(b) detecting a hybridization product.--

REMARKS

The Office Action of September 28, 2000, indicates that claims 1-14 and 16-33 are pending. Claims 1-14 and 16-33 have been cancelled herein without prejudice to or disclaimer of the subject matter contained therein. Claims 34-55 have been added. No new matter has been added by way of the above claim amendments.

Sequence Identification and Support for Claim Limitations

The relationship between nucleotide or amino acid sequences are illustrated in the attached Figure (Exhibit 1). Correspondence between recited sequences and Semaphorin proteins is as follows:

- nucleotide sequence SEQ ID NO:1 - rat Semaphorin W-encoding nucleic acid molecule;
- nucleotides 76 to 2406 of sequence SEQ ID NO:1 - CDS portion of rat Semaphorin W-encoding nucleic acid molecule
- nucleotide sequence SEQ ID NO:4 - human Semaphorin W-encoding nucleic acid molecule (C-terminal)
- nucleotides 1 to 1761 of SEQ ID NO:4 - human Semaphorin W-encoding nucleic acid molecule (C-terminal of CDS)
- nucleotide sequence SEQ ID NO:10 - human Semaphorin W-encoding nucleic acid molecule (N-terminal)
- amino acid sequence SEQ ID NO:3 - rat Semaphorin amino acid sequence
- amino acid sequence SEQ ID NO:6 - human Semaphorin W amino acid sequence (C-terminal)
- amino acid sequence SEQ ID NO:11 - human Semaphorin W amino acid sequence (N-terminal)
- nucleotides 259-1776 of SEQ ID NO. 1 encode a Semaphorin domain and correspond to amino acids 62-567 of SEQ ID NO:3, as described at page 54, line 4 of the specification.

Exhibit 1, attached, is a schematic showing the relationship among some of the sequences recited in the claims.

Hybridization conditions recited in the claims are described at page 20, lines 7-9 of the specification. Degrees of sequence identity recited in the claims are described at page 20, lines 23-24. The limitation on length of the nucleotide sequence of 27 or more (claim 51) is supported by the lengths of the sequences shown in the Sequence Listing; SEQ ID NO. 9 is 27 nucleotides long. Nucleic acid molecules comprising a part of a sequence disclosed in the specification are used in the cloning of Semaphorin W, northern hybridization, or the preparation of fragments of Semaphorin W cDNA in the working Examples of the specification.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 2, 3 and 7-10 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are respectfully requested.

The Examiner states as follows:

> The phrase "SEQ ID No. 4 or 5 and/or the base sequence shown in SEQ ID No. 10" in claim 2(e) line 8 is vague and renders the claim indefinite.
>
> The term "stringent conditions" in claims 2, 3 and 7 is vague and renders the claim indefinite.

Claims 2, 3 and 7-10 have been cancelled. Newly added claims 33 and 34 clearly show the relationships between the sequences, rendering this rejection moot.

Rejections under 35 U.S.C. § 112, First Paragraph

Written Description

Claims 1-3, 5, 7-10 and 17 are rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of adequate written description of the invention. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

The Examiner asserts in essence that the specification fails to describe those features of the genus of "Semaphorin domain"-containing proteins that define the genus. This is simply incorrect.

The Examiner states:

> … in view of the fact that the art does not provide an accepted definition of the term "gene" for semaphorin genes, … (page 5, lines 15-16)
>
> The scope of the claim includes numerous structural variants of semaphorin protein, and the genus is highly variant because a significant number of structural differences between genus members is permitted. (page 4, lines 15-17)
>
> …Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. (page 5, lines 5-6)
>
> With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides,… (page 6, lines 6-8)

The term "gene" has been changed to "isolated nucleic acid molecule" throughout the claims, clarifying the claims and obviating this basis for the rejection.

In new claims 35 (former claim 2) and 36 (former claim 3), and claims 37-40, the isolated nucleic acid molecule is one that encodes a protein having "Semaphorin domain" which is well-known in the art as a characteristic structure of Semaphorins.

As described in detail in the specification at page 23, line 10 to the last line, a "Semaphorin domain" is well-known in the art as a domain consisting of 300-600 amino acid residues and is characterized by a plurality of partial amino acid sequences commonly conserved among Semaphorin molecules. The number and position of cysteine residues is especially conserved among Semaphorin domains. (*See*, Exhibit 2, attached (*Neuron*, 14:941-948 (1995) at Fig. 1 (the Semaphorin domain is located between the handwritten arrows) and *Cell*, 75, 1389-1399 (1993), provided with the IDS of December 8, 1999, at Figs 3 and 4.)

Applicants note that the Examiner specifically criticizes the specification for failure to provide any alignment of sequences from which a description of a Semaphorin domain might be derived. This is not correct. The relevant description can be found at page 4, lines 11-17 of the specification, which reads:

> ...To date, more than 10 genes belonging to the Semaphorin family have been reported in a wide range of species covering insects... and viruses. These Semaphorins

characteristically contain in their amino acid sequences a certain structure called semaphorin domain consisting of about 500 amino acids (*Neuron*, 14, 941-948 (1995); *Cell*, 75, 1389-1399 (1993).

An excerpt from the *Neuron* reference is provided as Exhibit 2. As pointed out above, Figure 1 thereof is an alignment of five different proteins containing a Semaphorin domain. The Semaphorin domain defined by the alignment is clearly marked by the brackets in the figure (highlighted by hand-drawn arrows). Thus, a "Semaphorin domain" is well-known in the art of molecular neurobiology and is a structure sufficient to assign a protein as a member of Semaphorin family merely because the protein includes an amino acid sequence having high homology to the amino acids of a Semaphorin domain and includes the conserved cysteine residues. Accordingly, the skilled person in the art can easily envisage the detailed chemical structure of a Semaphorin domain and determine whether or not an isolated polynucleotide encodes all or part of a Semaphorin domain.

Further, the Semaphorin domain accounts for a considerable portion in the proteins having semaphorin activity (about 1/3 to 2/3) as shown in Exhibit 2 (see Figure). This suggests that the presence of a Semaphorin domain establishes a reasonable expectation that a given molecule will show semaphorin activity. Accordingly, a Semaphorin domain constitutes a structural feature that defines the genus of molecules of the present invention.

Additional claims 41-46 recite the claimed invention in terms of a functional limitation, i.e., possessing one of the biological activities described in Examples 8 and 9 (pages 60 ff. of the specification). The Examiner is reminded that the Written Description Guidelines published January 5, 2001 state that adequate written description of a claimed invention can be provided by either a structural or a functional feature that defines the genus of molecules encompassed by the claims. 66 F.R. 1099, 1106 at col. 2, line 36. See also col. 3, lines 22-23, indicating that functional features, when correlated with a structural feature (i.e. a Semaphorin domain) can also define a genus.

For all of the above reasons, Applicants submit that the present specification adequately describes the invention as presently claimed. Accordingly, the rejection of claims 1-3, 5, 7-10 and 17 are rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of adequate written description of the invention, should not be applied to the present claims.

Enablement

Claims 1-3, 5 and 7-10 stand rejected under 35 U.S.C § 112, first paragraph, for alleged lack of enabling disclosure in the specification. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

Claim 17 is also rejected for lack of enablement, but on a different basis. Here the Examiner asserts lack of enablement of

pharmaceutical utility. Claim 17 is canceled, rendering this particular rejection moot.

The Examiner admits that the present specification is enabling of claims limited to structures described by particular SEQ ID NOS. 1, 2 or 3. The Examiner takes a position that the present application does not enable one of ordinary skill in the art to identify variant structures that retain semaphorin activity.

Determination of enablement is to be a weighing of several factors, as enumerated in *Ex parte Forman*, 230 USPQ 547 (BPAI 1986). The factors to be considered are: the quantity of experimentation necessary, the amount of direction or guidance provided by the specification, the state of the prior art, the presence or absence of working examples, the nature of the invention, the relative skill of the worker in the art, the predictability of the art and the scope of the claims. *In re Wands* 8 USPQ2d 1400 (Fed. Cir. 1988), affirms these factors and further holds that the quantity of experimentation demanded is not determinative, the issue whether undue experimentation is needed to practice the full scope of the invention. *Wands* further establishes that, if the making of variants and screening them for activity is expected in the art to identify those that are operable, such screening is not undue experimentation if the relevant screen is described in the specification or known in the art. *Wands* at 1406.

While the Examiner enumerates the factors to consider, he relies entirely upon the unpredictability factor. Furthermore, the Examiner relies upon an incorrect aspect of unpredictability. The issue is not whether, as asserted by the Examiner, any imagined structure can be predicted *a priori* to be functional, but whether it is predictable that one of skill in the art, given one functional embodiment, can find another. Thus, the Examiner fails to establish a *prima facie* case for non-enablement and the rejection should be withdrawn on this basis alone.

Correct consideration of the *Forman* factors would reflect the following:

1. The invention is directed to cloned nucleic acids encoding a protein that has a defined structural characteristic, i.e. a semaphorin domain, or that has a recited biological activity, i.e. inhibiting neurite outgrowth or inhibiting growth cone formation.

2. The scope of the claims at issue is indeed generic, but constrained by either a stated degree of identity to a reference sequence or functionally by hybridization to a reference sequence under defined conditions. Some claims are limited functionally in terms of the biological activity of the protein encoded by the claimed nucleic acid.

3. The skill of the practitioner of molecular neurobiology is very high.

4. The specification provides description of essential features of a Semaphorin protein of the invention (or of a nucleic acid encoding it) both in terms of definition of a Semaphorin domain, at least one conserved amino acid residue, the complete open reading frame of one species of Semaphorin-encoding nucleic acid and biological activities associated with Semaphorin proteins of the invention. Thus the specification provides considerable guidance as to structural requirements for functional embodiments. The specification further provides guidance in the form of assays that can be used to test any particular embodiment for function.

5. The specification provides working examples of the isolation of nucleic acids encoding Semaphorin proteins and further provides working examples of assays that can be used to determine if any particular embodiment possesses one of the two biological activities recited in the claims.

6. The quantity of experimentation required to make variants of Semaphorin protein-encoding nucleic acids is not large by the standards of the art. The specification discloses at least one cloned DNA encoding an entire Semaphorin protein and kits are available commercially for performing mutagenesis along the entire length of the cloned DNA.

7. The quantity experimentation required to screen variants might be large, but again, not unexpected in the art. Variants can be screened by either of the assays described in Examples 8 and 9 of

the specification and the necessity for screening of variants is expected in the art. The state of the art is such that assays for semaphorin activity are well-known. For instance, a method for determining activity using dorsal root ganglion growth cones described in Exhibit 3 (see Fig. 6) has long been known in the art.

8. While it is unpredictable whether any particular variant would have one or more biological activities ascribed to Semaphorins, it is very predictable that any given mutation-screening experiment will allow isolation of functional variants.

Applicants submit that proper consideration of the factors for weighing enablement will result in withdrawal of the instant rejection.

In the event that the Examiner does not agree, Applicants further provide attached the Declaration 1 of Dr. Kimura, which shows that nucleic acid molecules comprising a Semaphorin domain, or having the activity of a Semaphorin protein as claimed, can be obtained by one of ordinary skill in the art by following the teachings of the specification. A signed copy of the Declaration will follow. Thus, whatever the Examiner's view of the subject, Applicants provide here objective evidence that the specification is enabling of practice of the present invention throughout the scope of the claims.

With regard to human Semaphorin W, the Examiner stated:

> …the nucleotide sequence of SEQ ID Nos. 4, 5, 7, and 10 are partial cDNA sequence of human semaphorin. …It is unclear whether human semaphorin would have the same

> function as the rat semaphorin W disclosed in the present application. It is also unclear whether any combination of SEQ ID No. 4, 5, and 10 in any order would encode a protein which functions as the rat semaphorin W protein as filed. (page 9, lines 6-13)

Claims 7-10, directed to a DNA cloned from a human cDNA library, are cancelled thus rendering the rejection moot. In any event, Applicants' understanding is that the Examiner questions whether or not a protein that does not encode a complete Semaphorin domain would nonetheless encode a functional protein. Applicants reserve the right to address this issue in a Continuation Application. The Examiner should note, however, that the peer-reviewed journal of the National Academy of Sciences has accepted the conclusion of a paper attached hereto as Exhibit 4, that the nucleic acid sequences of SEQ ID NOS: 4 and 10 (encoding the amino acid sequences of SEQ ID NOS: 6 and 11) constitute parts of the human homolog of rat Semaphorin cDNA.

For all of the above reasons, Applicants submit that the claimed invention should be considered enabled by the specification and the instant rejection should be withdrawn.

Rejections Under 35 U.S.C. § 102

Claims 1, 2, 5, 7 and 17 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Hillier et al., 1995 (hereinafter "Hillier et al."). This rejection is respectfully traversed. Reconsideration and withdrawal thereof are respectfully requested.

The Examiner stated:

> Hillier et al. teaches a human cDNA sequence, EST Accession No. R54387, which is 85.6% identical to base 1127-1551 of SEQ ID NO: 3. (page 12, last paragraph)

SEQ ID NO. 3 is an amino acid sequence, Applicants thus assume that the Examiner meant to refer to SEQ ID NO:1 in the rejection, not SEQ ID NO:3.

This rejection is not warranted. R54387 is an EST fragment of 424 base pairs which can encode a protein of only about 140 amino acids. Such a protein certainly cannot encode a "Semaphorin domain" consisting of about 500 amino acids. Lacking a Semaphorin domain, any protein encoded by R54387 would not be expected to have the functions of inhibiting growth cones or inhibiting neurite outgrowth as recited in the present claims. Because the sequence of R54387 is only 424 bases, it is also clear that R54387 does not exhibit 80% or more, let alone 90% or more, identity with any sequence set forth in the present claims. Accordingly, Hillier et al. does not destroy the novelty of the present claims and the instant rejection should be withdrawn.

Rejections Under 35 U.S.C. § 103

Rejection Under 35 U.S.C. § 103(a)

Claims 8-10 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ohgi et al., 1991 (hereinafter Ohgi et al.) in view of Hillier et al. The rejection is traversed as it might be applied

to the present claim 48, directed to similar subject matter. Reconsideration and withdrawal thereof are requested.

That Hillier does not describe any element of the present invention is explained above. Ohgi does not remedy the deficiencies of Hillier in providing any isolated nucleic acid that encodes a Semaphorin domain or any protein having the biological activity of a Semaphorin protein. As this element is lacking from the combined references, the Examiner fails to establish *prima facie* obviousness of the invention of claim 48.

Applicants submit that the present application well-discloses and claims patentable subject matter. The favorable action of allowance of the pending claims and passage of the application to issue are respectfully requested.

If there are any minor matters precluding allowance of the application which may be resolved by a telephone discussion, the Examiner is respectfully requested to contact Mark J. Nuell, Ph.D. (Reg. No. 36,623) at (703) 205-8000.

Pursuant to 37 C.F.R. § 1.17 and 1.136(a), Applicants respectfully petition a three (3) month extension of time for filing a response in connection with the present application. The required fee of $890.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees

required under 37 C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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VERSION TO SHOW MARKED CHANGES

Claims 1-14 and 16-33 have been cancelled without prejudice or disclaimer of the subject matter contained therein.

Claims 34-55 have been added.